Remarks / Arguments

The applicant herein responds to the Office action mailed October 3, 2005. The applicant submits the following papers with this transmission: 1) Facsimile Cover Sheet; 2) Certificate of Transmission under 37 CFR 1.8 (PTO/SB/97); 3) Transmittal Form (PTO/SB/21); 4) a Petition for a Three Month Extension of Time (PTO/SB/22); and 5) the applicant's substantive Amendment and Response (25 pages).

The Office action set a three-month Shortened Statutory Period of until January 3, 2006, for submission of a responsive communication. Applicant's response is thus timely in view of the aforementioned petition for extension of time until April 3, 2006.

The applicant authorizes the Director to charge, or credit any overpayment, to USPTO Deposit Account (No.: 50-0244) associated with this communication.

In the applicant's June 7, 2005, Amendment and Response the applicant: 1) canceled, without prejudice, claims 37-45, 47, 53, and 55; and 2) amended claims 18-33, 35, 48, 50, and 52. Thus, claims 18-36, 46, 48-52, 54, 56, and 57 are pending and under examination.

In this communication, applicant has herein amended claims 18, 22-32, 35, 46, 48-5, and 57 without prejudice and without acquiescence to the Examiner's arguments (for the reasons stated herein). The amendments to the claims are fully supported by the Specification and do not add new matter. Their entry is respectfully requested. Applicant has also canceled claims 52 and 54 for the reasons stated herein.

In response to the applicant's remarks and amendments submitted in his June 7, 2005, Amendment and Reply, the Examiner has herein withdrawn, as moot or overcome, numerous rejections. Paragraphs 6-41, respectively, of the present Office action describe the rejections that have been withdrawn.

The present Office action however sets forth various new and/or maintained objections and rejections. In view of the number and complexity of rejections as well as for the Examiner's convenience, the applicant herein provides a listing of currently pending objections/rejections:

I. Claim 26 remains rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite (Office action, ¶ 42);
II. Claims 49 and 50 remain rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite (Office action, ¶ 43);
III. Claim 19 remains rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite (Office action, ¶ 44);

IV. Claims 52 and 54 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter (Office action, ¶ 45);
V. Claim 48 remains rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter (Office action, ¶ 46);
VI. Claims 18-33 and 51 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious under McMaster (U.S. 6,146,902) in view André *et al.* (In: Modern Vaccinology, (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, NY, *pp.* 41-54, (1994)), Levine *et al.* (In: Abstracts of the Tenth International Pathogenic *Neisseria* Conference, (Ed) Zollinger *et al.* Baltimore, MD, *pp.* 228-230 (1997)), and Lindberg (Vaccine, 17:S28-S36 (1999)) (Office action, ¶ 47);
VII. Claims 18-36, 46-51, 56, and 57 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious under Costantino *et al.*, (Vaccine, 10:691-698 (1992)) in view of McMaster, André *et al.*, Levine *et al.*, and Lindberg (Office action, ¶ 48);
VIII. Claims 52 and 54 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious under Costantino *et al.*, and McMaster, in view of André *et al.*, Levine *et al.*, Lindberg, and Avendano *et al.*, (Pediatric Infect, Dis. J., 12:638-643 [1993]) (Office action, ¶ 49);
IX. Claims 35 and 36 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter (Office action, ¶ 50);
X. Claim 49 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter (Office action, ¶ 51);
XI. Claims 46 and 48 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter (Office action, ¶ 52); and
XII. Claims 18-36, 46, 48-52, 54, 56, and 57 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite (Office action, ¶ 53).

The applicant respectfully submits that the amendments and remarks presented herein: 1) overcome all of the objections and rejections presented in the October 3, 2005, Office action; 2) advance the prosecution of the present application; and 3) place the application in condition for allowance.

The Objections to the Specification

The Office action cites 35 U.S.C. § 132 and its prohibition against new matter, in the objection to the applicant's amendments to the Specification submitted in his June 7, 2005 responsive communication.

The Examiner makes the following arguments concerning the Specification amendments. First, it is argued that "Neither the generic limitation [1] 'saponin adjuvants', nor the narrower limitation [2] 'QS-7' are supported in the Specification, as originally filed." (Office action, ¶ 5). As to assertion (1), respectfully, the applicant's amendment does not constitute new matter

since the applicant is allowed under the authority of 37 C.F.R. §§ 1.57(d) and 1.57 (b) *et seq.*, to incorporate by reference nonessential material.[1] Paragraph 22 of the applicant's Specification specifically reserved the right to incorporate by reference essential, and nonessential material, by material pursuant to 37 C.F.R. § 1.57 (b) *et seq.*[2] Pending claim 35, has been amended to remove the term "saponin" recited therein in order to further his business interests and to advance expedite prosecution, yet without acquiescing to the Examiner's arguments and, furthermore, while reserving the right to prosecute deleted subject matter in the future. The Examiner is respectfully directed to the applicant's discussion of rejection IX for further remarks concerning claims 35 and 36. Respectfully, since the term "saponin" has been removed from pending claim 35, the term "saponin" is not even essential matter as defined in 37 C.F.R. § 1.57 (c)(1).[3]

Nonetheless, applicant submits that the recitation of "saponin adjuvant" in the June 7, 2005, communication merely names the class to which the exemplary, and originally recited, QS-21 adjuvant belongs. One skilled in the art at the time of invention would clearly understand that QS-21 is among "saponin adjuvants." Moreover, paragraph 33 teaches: 1) that the provided list is exemplary and not intended to be limited to the specifically recited adjuvants, by stating, "Adjuvants include, by way of example and not limitation . . . ."; and 2) that one skilled in the art was directed to consider standard texts in the field for additional suitable adjuvant(s). Importantly, applicant provided citation to an exemplary text in the adjuvant field "*See, e.g.*, Vaccine Design, the Subunit and Adjuvant Approach, 1995 (M. F. Powell and M. J. Newman, eds., Plenum Press, N.Y.)." (Specification, ¶ 33, *ll.* 9-10 and 13-15, respectively, as published US 2003/0068336 A1). Powell and M. J. Newman describe at length various potentially suitable

[1] *See*, 37 C.F.R. § 1.57(d), stating, "Other material ('Nonessential material') may be incorporated by reference to U.S. patents, U.S. patent application publications, foreign patents, foreign published applications, prior and concurrently filed commonly owned U.S. applications, or non-patent publications."

[2] *See*, 37 C.F.R. § 1.57(b), stating, "Except as provided in paragraph (a) of this section, an incorporation by reference must be set forth in the Specification and must: (1) Express a clear intent to incorporate by reference by using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"); and (2) Clearly identify the referenced patent, application, or publication."

[3] *See*, 37 C.F.R. § 1.57(c)(1)-(3), stating, "(1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112; (2) Describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 U.S.C. 112; or (3) Describe the structure, material, or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of 35 U.S.C. 112."

adjuvants. In particular, Powell and Newman describe saponin adjuvants, related compounds, and many other types and classes of adjuvant compounds, in its various sections.[4]

In regard to assertion (2) concerning "QS-7" being new matter, applicant respectfully points out that "QS-7" is not presently recited in the claims. Thus, the assertion that "QS-7" is new matter, which is determined in view of the claimed subject matter pursuant to 37 C.F.R. § 1.57(c)(1)-(3), is inaccurate. Furthermore, applicant's recitation of "QS-7" in his communication of June 7, 2005, was merely one permissible further exemplification of potentially suitable saponin adjuvants already exemplified in the recitation to QS-21. This exemplification, as described above, is allowed for by the C.F.R. and fully supported by incorporation of Powell and Newman's text wherein "QS-7" is described at *p.* 526 as are other potentially suitable highly purified extracts from *Quillaja saponaria* Molina tree (*e.g.*, QS-17, QS-18, and Quil-A).

Second, the Examiner further argues that the applicant's amendments to the Specification in the June 7, 2005, communication add new matter because:

> The current exemplication for 'pcpp': '(e.g., Poly[bis(carboxylatophoxy)phosphazene] and/or Poly[di(carboxyatophoxy)phosphazene])' is new matter. No authoritative source, such as, a standard textbook or a commercial catalogue that equates the recited trademark or abbreviated adjuvants to the newly added generic descriptions, is provided to establish that what is now added does not constitute new matter.

(Office action, ¶ 5). Applicant must respectfully disagree with the Examiner's assertion that nothing equates "the recited trademark or abbreviated adjuvants to the newly added generic descriptions" as stated by the Examiner. As noted above, the originally filed Specification, in paragraph 33 in question, clearly directed skilled artisans to Powell and Newman's text wherein Chapter 20 entitled: "*Water-Soluble Phosphazene Polymers for Parental and Mucosal Vaccine Delivery*", *pp.* 473-493, is directed to describing the chemistry and biological activity of polyphosphazens notably including PCPP (poly[di(carboxyatophoxy)phosphazene]) and PCGPP. (*See*, Powell and Newman, *p.* 476). Likewise, poly[bis(carboxylatophoxy)phosphazene, is described in a paper by H.R. Allcock and S. Kwon (H.R. Allcock and S. Kwon, Macromoleculaes, 22:75-79 (1989)) cited as a reference at *p. 492* of Chapter 20.

[4] *See*, Vaccine Design, the Subunit and Adjuvant Approach, 1995 (M. F. Powell and M. J. Newman, eds., Plenum Press, N.Y., saponins generally, *pp.* 422, 560, and 575; saponin QS-21, *pp.* 356, 525-541, 721, 833, 925; Quil A, *pp.*

Furthermore, applicant respectfully asserts that providing commonly known chemical names in an amendment to the Specification for the compounds associated with the acronym "pcpp" adjuvant is analogous to the permissible action deemed by the Federal Circuit to be "merely renam[ing]" of an otherwise known and identified compound in the *Scarring Corp. v. Megan, Inc.*, decision. (*See*, Scarring Corp. v. Megan, Inc., 222 F.3d 1347, 1352-1353 (Fed. Cir. 2000), *see also* MPEP §2163.07).

For the above stated reasons, applicant respectfully asserts the amendments to the Specification submitted on June 7, 2005, do not add new matter. Accordingly, the objection to the Specification should be withdrawn.

Claim Rejections

I-III. The Indefiniteness Rejections

A. Claim 26

The Examiner states claim 26, and claims 27 and 28 dependent thereon, are indefinite because "The claim continues to refer to serogroup A or serogroup C as 'serogroups' as opposed to serogroup." (Office action, ¶ 42). Applicant has corrected the typographical error in pending claim 26.

B. Claims 49 and 50

The Examiner states claims 49 and 50 are indefinite for reciting the term "derived" as was argued in the previous Office action. (Office action, ¶ 43). The Specification however provides support for the term "derived," for example, Specification *pp.* 23-26 and 46-55 support the applicant's use of the term "derived." Nonetheless, without acquiescing to the Examiner's arguments, applicant herein reiterates his willingness to advance the prosecution by removing the term "derived" from claims 49 and 50. This was the applicant's previous intention, however, because of an inadvertent omission the amendment was not formally entered in the June 7, 2005, communication.

72, 210, 422, 543 and 825; *see also*, ISCOMs, *pp.* 543-558.

C. Claim 19

The Examiner states claim 19, and claims 20 and 21 dependent thereon, are indefinite for reciting the term "derived" as was argued in the previous Office action. (Office action, ¶ 44). In particular the Examiner states, "the rejection of claim 19 . . . is maintained . . . . The claim as amended, does not, include the suggested amendment and continues to have the limitation, 'from *N. meningitidis* serogroup . . . .'" (Office action, ¶ 44). Applicant submits that the above suggested claim amendment was indeed entered in his June 7, 2005, communication. Applicant confirmed this assertion by checking the "Image File Wrapper" available at the USPTO PAIR system showing pending claim 19 was amended, in pertinent part, as the Examiner suggested to recite "*N. meningitidis* serogroup of A or C."

In view of the above-mentioned remarks and amendments, applicant submits that the Examiner's concerns stated in rejections I-III have been sufficiently addressed herein. Accordingly, applicant respectfully requests that these rejections be withdrawn.

IV-V. The New Matter Rejections

A. Claim 52 and 54

Claims 52 and 54 stand rejected as allegedly containing new matter as set forth in the previous Office action. (Office Action, ¶ 45). Applicant respectfully cannot agree with the Examiner's arguments and conclusions. The Examiner's arguments concerning this rejection as set forth at ¶ 45 of the Office action are provided, in pertinent part, below:

> **Applicant is correct in that claim limitations can be supported in the Specification through express, implicit, or inherent disclosure. Applicant is also correct in that the Specification teaches sterile liquids.** However, the claim limitation at issue is a structural limitation, which recites that the sterile liquid is 'contained within a single use syringe' or 'contained within a vial'. With regard to the treatise, the Specification states that standard texts 'such as' 'REMINGTON'S PHARMACEUTICAL SCIENCE, 17th edition, 1985, incorporated herein by reference, 'may' be consulted 'to prepare suitable preparations' without undue experimentation. The recitation in the Specification with regard to REMINGTON'S PHARMACEUTICAL SCIENCE is limited to "preparing suitable preparations' which does not provide descriptive

> support, or express, implicit, or inherent disclosure for the now added structural claim limitations that are identified above.

(Office action, ¶ 45, emphasis added). The Examiner notably makes several admissions: 1) "claim limitations can be supported in the Specification through express, implicit, or inherent disclosure"; and 2) the "Specification teaches sterile liquids."

Despite the Examiner's agreement with the applicant's remarks in his June 7, 2005, communication, the rejection was maintained in the present Office action.

Claims 52 and 54 are dependent upon claim 51, which recites an immunological composition of claim 33 formulated as a sterile liquid. Claim 51 itself does not stand rejected as containing new matter. Applicant respectfully submits that Claims 52 and 54 do not add new matter and are supported by the Specification in numerous places. (*See*, Specification, ¶¶ 38-45). For example, the Specification states that:

> Compositions of the invention can include liquid preparations . . . and, preparations for parenteral, subcutaneious, intradermal, intramuscular, intraperitoneal or intravenous administration (e.g., injectable administration), such as sterile suspensions or emulsions. Intravenous and parenteral administration are preferred. Such compositions may be in admixture with a suitable carrier, diluent, or excipient such as sterile water, physiological saline, glucose or the like. The compositions can also be lyophilized. The compositions can contain auxiliary substances such as wetting or emulsifying agents, pH buffering agents, gelling or viscosity enhancing additives, preservatives, flavoring agents, colors, and the like, depending upon the route of administration and the preparation desired. Standard texts, such as "REMINGTON'S PHARMACEUTICAL SCIENCE", 17Th edition, 1985, incorporated herein by reference, may be consulted to prepare suitable preparations, without undue experimentation.

(Specification, ¶ 38, emphasis added). The Specification provides support for sterile preparations contained and administered from various injectable embodiments, formulations, and containers. Furthermore, as noted previously, the Specification incorporated by reference *Remington's Pharmaceutical Science* 17th (1985).[5] Applicant respectfully submits one skilled in art relating to pharmaceutical, vaccinal, and/or human therapeutics would clearly understand the above-

[5] *Remington's Pharmaceutical Science* has since been renamed *Remington: The Science and Practice of Pharmacy.*

mentioned treatise in combination with the teachings of the Specification as providing "express, implicit, or inherent disclosure" for the respective subject matter at issue.[6]

Notably, in regard to pending claim 52, *Remington's Pharmaceutical Science* 19th Ed. (1995) (the oldest edition of this treatise currently available to the applicant) states: 1) at Vol. 1, Part 8 *Pharmacy Practice*, Chapter 107, *Health Accessories*, section entitled: *Hypodermic Equipment, pp.* 1856-1857, the reference describes various apparatus and techniques concerning "subcutaneously (under the skin) or intradermally, intravenously (into a vein) or intramuscularly (into the muscle)"; and 2) at Vol. 1, Part 8 *Pharmacy Practice*, Chapter 107, *Health Accessories*, section entitled: *Hypodermic Equipment, p.* 1856, Fig. 24, the reference states "Hypodermic syringes. Left, tuberculin or vaccine syringe. . . ." (*See, Remington's* 19th Ed., (1995), Vol. 1, Part 8, Chap. 107, *pp.* 1856-1857; *See also, p.* 1856, Fig 24).

In regard to pending claim 54, likewise, *Remington's* 19th Ed., Chap. 87, *Parenteral Preparations, pp.* 1524-1548, describes many of the factors one skilled in the art would consider when preparing suitable preparations of parenteral administration. In particular, the Examiner's attention is drawn to the Section entitled: *Components and Containers, pp.* 1526-1533, which describes various suitable containers for injectable parenteral preparations including various types of vials.

Applicant notes, that the Examiner's comment "Applicant opines that *In re Rasmussen* is not dispositive on the issue" does not seek correct an allegedly incorrect interpretation of the *Rasmussen* decision. (Office action, ¶ 45).

Nonetheless, applicant has chosen to cancel claims 52 and 54 without prejudice. Applicant cancels these claims in order to advance the prosecution and his business interests, yet without acquiescing to the Examiner's arguments and conclusions, and while reserving the right to prosecute claims directed to the same, or similar, subject matter in the future. Thus, the instant rejection of claims 52 and 54 is moot.

[6] *See,* MPEP § 2163(I)(B) acknowledging that newly added claim terms can be "*supported in the Specification through express, implicit, or inherent disclosure.*" (emphasis added).

B. Claim 48

Claim 48 stands rejected as allegedly containing new matter as set forth in the previous Office action. (Office Action, ¶ 46). Applicant respectfully cannot agree with the Examiner's arguments and conclusions.

Applicant submits that, as above, the Examiner's arguments appear to be impermissibly predicated upon the faulty assertion that the Specification must provide verbatim "*in haec verba*" recitation and support for every presently claimed element.

Nonetheless, in order to advance prosecution and his business interests, yet without acquiescing to the Examiner's arguments and conclusions, and while reserving the right to prosecute claims directed to the same, or similar, subject matter in the future, applicant herein amends claim 48 to recite inactivated bacterial toxins as mentioned in the current Listing of Claims.

The present amendments to claim 48 are fully supported in the Specification, for example, at Specification ¶ 29, and do not add new mater. The entry of the amendments to claim 48 is respectfully requested, as is the withdrawal of this rejection.

Applicant has also amended claims 49 and 50, that dependent on claim 48, for similar reasons, and in order to better define certain embodiments of the present invention. Claims 49 and 50 do not add new matter and are supported by the Specification, for example, Specification ¶ 29.

VI-VIII. The Obviousness Rejections

Pending claims, 18-36, 46, 48-51, 56, and 57, remain rejected as allegedly obvious under one or more combinations of the cited references. Claims 52 and 54 were not rejected as being obvious under any combination of these references. Applicant must again respectfully disagree with the Examiner's arguments and conclusions for the reasons stated herein and those previously made of record.

The Federal Circuit requires factual support for all obviousness rejections by the establishment of three indispensable criteria in each rejection. Failure to establish even one of the criterion necessitates withdrawal of the rejection. The criteria were collectively developed to prevent the impermissible use of hindsight during examination. MPEP § 2143 *et seq.* describes the three criteria as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings [MPEP § 2143.01]. Second, there must be a reasonable expectation of success. [MPEP § 2143.02] Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations [MPEP § 2143.03].

Applicants respectfully submit the Examiner has not sufficiently provided the request **objective evidence** for establishing the *prima facie* obviousness of the present claims under the cited combinations of references for the following reasons.[7]

A. Claims 18-33 and 51

Claims 18-33 and 51 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious under McMaster (U.S. 6,146,902) in view André *et al.* (In: Modern Vaccinology, (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, NY, *pp.* 41-54, (1994)), Levine *et al.* (In: Abstracts of the Tenth International Pathogenic Neisseria Conference, (Ed) Zollinger *et al.* Baltimore, MD, *pp.* 228-230 (1997)), and Lindberg (Vaccine, 17:S28-S36 (1999)). (Office action, ¶ 47). The Examiner's attention is respectfully directed to the discussion of the non-obviousness of these claims provided in the remarks below.

B. Claims 18-36, 46-51, 56, and 57

Claims 18-36, 46-51, 56, and 57 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious under Costantino *et al.*, (Vaccine, 10:691-698 (1992)) in view of McMaster, André *et al.*, Levine *et al.*, and Lindberg. (Office action, ¶ 48).

Applicant's remarks addressing the rejection of claims 18-33 and 51 are being combined with those addressing the rejection of claims 18-36, 46-51, and 57 because: 1) each rejection, respectively, can be overcome by establishing the non-obviousness of independent claim 18; and 2) the rejection over claims 18-36, 46-51, and 57 is over nearly the same combination of references as that over claims 18-33 and 51, with the notable addition of Costantino *et al.* to the

[7] *In re Lee*, 277 F.3d 1338, 1342, 61 USPQ2d 1430 (Fed. Cir. 2003) (holding, "[obviousness rejections] **must be based on objective evidence of record**. This precedent has been reinforced in **myriad decisions**, and **cannot be dispensed with**." emphasis added).

latter combination. Thus, overcoming the combination of references cited against claims 18-36, 46-51, and 57 necessarily also overcomes the rejection over claims 18-33 and 51.

Applicant wishes to address two initial matters before turning to the non-obviousness of the present claims.

First, applicant notes the Examiner comment that "the references of McMaster, Levine *et al,* Andre *et al.* and Lindberg are applied in a rejection under 35 U.S.C. § 103. . . . One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references [citations omitted]." (Office action, ¶ 47). Applicant also respectfully submits, however, that "When analyzing a patent claim for obviousness, the claim should be considered as a whole, but the differences between the claim and the prior art need to be identified to place the obviousness analysis into proper perspective." (*See, Ryko Manufacturing Co., v. Nu-Star, Inc.*, 950 F.2d 714, 21 USPQ2d 1053 (Fed. Cir. 1991)).

Second, the Examiner states "The rejection based on the disclosure of Granoff (WO 98/58,670) was withdrawn as indicated via paragraph 13 of the Office Action mailed 12/07/04. Applicant is reminded that the Office is not required to provide rebuttal to Applicant's arguments on a rejection that is moot." (Office action, ¶ 47). Applicant reiterates his appreciation for withdrawn of that rejection. However, applicant's remarks concerning the state of the art recognized by Granoff '670 are still relevant to the complete picture that the Examiner is required to consider when establishing the substantive evidence request for a *prima facie* conclusion of obviousness. Notably, the meningococcal serotype distribution and disease occurrence at the time of '670 publication makes the omission of the Y and W-135 serogroups "conspicuous and significant", as stated previously by the applicant. Indeed, the '670 reference acknowledges the licensure of a tetravalent (A, C, Y, and W-135) meningococcal polysaccharide vaccine composition. (*See*, Granoff, '670, *p.* 2, *ll.* 19-23).

Furthermore, the applicant must respectfully submit that the Examiner's argument that "Andre *et al.*, Levine *et al.* or Lindberg do not have to teach detailed tables, graphs, or protocols concerning meningococcal vaccine production. Lindberg does not have to definitively specify the quantity or quality of any data considered. Andre *et al.* do not have to describe one vaccine technology that is more promising than the other" is contrary to the law. It is well settled that before the purported teachings of a reference can be considered for use in an obviousness

rejection, the reference(s) itself must sufficiently teach one skilled in the art how to make and use the compositions and/or methods allegedly disclosed therein pursuant to § 112. For example, in a case directly on point, the Federal Circuit in *Beckman Instruments, Inc., v. LKB Produkter AB*, held that "In order to render a claimed apparatus or method obvious under Section 103, the prior art must enable one skilled in the art to make and use the apparatus or method." (*Beckman Instruments, Inc., v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) emphasis added). Applicant points to this case as continued support for his assertions that there was motivation for reasonably successfully combining the cited references.

The Examiner apparently continues to **trivialize** the unpredictability in the field of biologics and vaccines. Until the applicant's invention, it was not taught or suggested in the art that meningococcal Y and/or W-135 serogroup polysaccharide-protein conjugates could be combined in a composition, no less was there a teaching that these conjugates comprising these serogroups could be combined without deleterious side effects or suppression of immunogenicity of any one or more, or potentially all of the respective meningococcal serogroup polysaccharide-protein carrier conjugates present in the composition.

For example, S. Gizurarson, in a 1998 paper, entitled "*Clinically Relevant Vaccine-Vaccine Interactions; A guide for Practitioners*," describes a great number of adverse interactions and failed vaccine development attempts. (Attachment A). Importantly, the paper reported that an attempted combination of meningococcal polysaccharides A and C serogroups vaccines with a measles vaccine caused the immunogenicity of the measles vaccine to be suppressed "The meningococcal seroconversion was unaffected, but the immunogenicity of the measles vaccine was significantly depressed."[8] S. Gizurarson, further states "The interactions may occur because of physical or chemical interactions within the vaccine formulation, interactions between live vaccines or immunological interference." (*See*, S. Gizurarson, BioDrugs (1998) Summary).

In contrast to assertion of triviality apparent in the pending obviousness rejections concerning the vaccinal arts, those skilled in the vaccinal arts do not treat the difficulties and lack

[8] *See*, Sveinbjön Gizurarson, *Clinically Relevant Vaccine-Vaccine Interactions; A guide for Practitioners*, BioDrugs, Jun; 9(6):443-453, *pp.* 448-449 (1998)).

of predictability associated with vaccine conception, formulation, production, and administration with such triviality.

Moreover, given the epidemiology of meningococcal disease and the meningococcal serotype distribution, one skilled in the art should be able to trivially produce—given the triviality in the Examiner's arguments—a successful meningococcal serogroup B polysaccharide-carrier protein vaccine conjugate. The fact of the matter is that, however, B serogroup conjugates have proven very difficult for those skilled in the art to produce. Meningococcal B serogroup polysaccharide-carrier protein conjugates currently have only been developed for small scale relatively isolated and unique populations.

In sum, at best as previously asserted, it may have been obvious to try to develop the applicants presently claimed compositions, however, this does not establish the objective evidence required for *prima facie* obviousness. The Federal Circuit has repeatedly held that using an obvious to try rational is a legally impermissible basis for attempting to establish a motivation to combine references especially in unpredictable fields such as immunology and vaccinology.[9]

C. Claims 52 and 54

As stated above, the rejection of claims 52 and 54 is moot.

IX-XI. The New Matter Rejections

A. Claims 35 and 36

The Examiner argues, "Claim 35, as amended, further includes the added limitations: '(N-2-Deoxy-2-L-leucylamino hydroacetate', '(3-cholesterol)', 'Poly[bis(carboxylatophoxy)phosphazene] and/or Poly[di(carboxyatophoxy)phosphazene])', which constitute new matter." (Office action, ¶ 50).

[9] "An 'obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." (*In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 [Fed. Cir. 1990]; emphasis added); "Obvious to [try] is not a proper standard for obviousness. . . . [S]elective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings." (*In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 [Fed. Cir. 1988], emphasis added).

As an initial matter, and in further view of applicant's remarks concerning the Objections to the Specification, the claim terms "(N-2-Deoxy-2-L-leucylamino hydroacetate," "(3-cholesterol)," "Poly[bis(carboxylatophoxy)phosphazene] and/or Poly[di(carboxyatophoxy)phosphazene])" were entered, without acquiescence, in applicant's June 7, 2005, communication partially in view of the December 7, 2004, Office action, ¶ 20(o) indefiniteness rejections over claims 35 and 36. In pertinent part, the ¶¶ 20(o) and (p) rejections stated:

> (o) Claim 35 is vague and indefinite inn the use of abbreviations in the claim language: 'pcpp', 'DC-chol', CpG' and 'BAY' . . . . It is suggested that each abbreviation be recited as a full terminology at [the] first occurrence in the claim, with the abbreviated recitation recited in parentheses.

(December 7, 2004, Office action, ¶ 20(o)). Applicant amended claims 35 and 36, in part, to recite the "full terminology" for the respective abbreviations known and recognized in the art for the instant subject matter set forth in the Specification and then claimed. The "full terminology" explaining these terms is not new matter.

Claim 35, and claim 36 dependent thereon, stand rejected as allegedly containing new matter. (Office action, ¶ 50). In particular, "the added limitations 'saponin" and 'QG-21' in claim 35, as amended, are new matter. (Office action, ¶ 50, emphasis added). For the reasons stated above, applicant respectfully cannot agree with the Examiner's arguments or conclusions.

Nonetheless, in order to advance prosecution and his business interests, yet without acquiescing to the Examiner's arguments and conclusions, and while reserving the right to prosecute claims directed to the same, or similar, subject matter in the future, applicant herein amends claim 35 to remove the term "saponin."

As to the Examiner's argument that "QG-21" is new matter in claim 35, applicant respectfully notes that the typographical error converting the QS to QG has been corrected. Support for correcting the typographical error can be found in the Specification, for example, at ¶ 33. The amendment does not add new matter.

B. Claim 49

Claim 49 stands rejected as allegedly containing new matter. (Office action, ¶ 51). Applicant respectfully cannot agree with the Examiner's arguments or conclusion. Nonetheless, applicant submits the amendments made to claim 49, described above, render the instant rejection moot.

C. Claims 46 and 48

Claims 46 and 48 stand rejected as allegedly containing new matter for the recitation of a "'single protein species'. However, the descriptive support in the Specification as originally filed is limited to a 'single carrier protein species' (see paragraph 0026). The full scope of the broad limitation 'single protein species' is not supported by the instant Specification." (Office action, ¶ 52). Again, applicant respectfully cannot agree with the Examiner's arguments or conclusion.

Nonetheless, in order to advance prosecution and his business interests, yet without acquiescing to the Examiner's arguments and conclusions, and while reserving the right to prosecute claims directed to the same, or similar, subject matter in the future, applicant herein amends claims 46 and 48 to recite the term "single carrier protein species." As pointed out by the Examiner, this term is fully supported and does not add new matter.

In view of the above stated remarks and claim amendments, applicant respectfully submits that each of the Examiner's stated concerns in rejection ¶¶ 50, 51, and 52 have been overcome. The withdrawal of these rejections is therefore respectfully requested.

XII. The Indefiniteness Rejections

The Examiner has made various indefiniteness rejections over claims18-36, 46, 48-52, 54, 56, and 57. The rejections at issue are set forth at ¶¶ 53(a)-(q). Rejection of claim 52 and 54 under this section is moot as these claims have been canceled for other reasons. Applicant addresses the Examiner's concerns in the order in which they were presented. (Office action, ¶ 53).

(A) Claim 18 (Office action, ¶ 53(a))

Applicant has amended claim 18, without prejudice or acquiescence to the Examiner's arguments, as described in the Listing of the Claims. The above-mentioned amendment to claim 18 makes this rejection moot.

(B)-(D) Claim 22 (Office action, ¶¶ 53(b)-(d))

Applicant has amended claim 22, without prejudice or acquiescence to the Examiner's arguments, as described in the Listing of the Claims. The above-mentioned amendments to claim 22 make this rejection moot.

(E) Claim 35 (Office action, ¶ 53(e))

Applicant has amended claim 35, without prejudice or acquiescence to the Examiner's arguments, as described in the Listing of the Claims. The above-mentioned amendment to claim 35 makes this rejection moot.

(F) Claim 22 (Office action, ¶¶ 53(f))

Applicant has amended claim 22, without prejudice or acquiescence to the Examiner's arguments, as described in the Listing of the Claims. The above-mentioned amendments to claim 22 makes this rejection moot.

(G)-(H) Claims 23, 24, 25, 27, 28, 29, and 33 (Office action, ¶¶ 53(g) and (h))

Applicant has amended claims 23, 24, 25, 27, 28, 29, and 33, without prejudice or acquiescence to the Examiner's arguments, as described in the Listing of the Claims. The above-mentioned amendments to claims 23, 24, 25, 27, 28, 29, and 33 make these rejections moot.

(I) Claim 29 (Office action, ¶¶ 53(i))

Applicant respectfully cannot agree with the Examiner's argument or conclusion. Applicant respectfully submits that the Markush groupings in pending claim 29 are each

sufficiently definite and unlikely to confuse one skilled in the art as to the scope of the claimed subject matter.

(J) Claims 30, 31, and 32 (Office action, ¶ 53(j))

Applicant has amended claims 30, 31, and 32, without prejudice or acquiescence to the Examiner's arguments, as described in the Listing of the Claims. The above-mentioned amendments to claims 30, 31, and 32 make these rejections moot.

(K) Claim 35 (Office action, ¶ 53(k))

Applicant has amended claim 35 as described above, without prejudice or acquiescence to the Examiner's arguments. The above-mentioned amendment to claim 35 makes this rejection moot.

(L) Claim 35 (Office action, ¶ 53(l))

Applicant has amended claim 35, as described in the Listing of the Claims, without prejudice or acquiescence to the Examiner's arguments. The above-mentioned amendment to claim 35 makes this rejection moot.

(M) Claim 35 (Office action, ¶ 53(m))

Applicant respectfully cannot agree with the Examiner's argument or conclusion. Applicant respectfully submits that the presently recited claim terminology is sufficiently definite and unlikely to confuse one skilled in the art as to the scope of the claimed subject matter.

(N) Claim 51 (Office action, ¶ 53(n))

Applicant has amended claim 51, as described in the Listing of the Claims, without prejudice or acquiescence to the Examiner's arguments. The above-mentioned amendments to claim 51 make this rejection moot.

(O) Claim 56 (Office action, ¶ 53(o))

Applicant respectfully submits that present claim 56 does not recite a Markush group as suggested by the Examiner. Thus this rejection is moot on its face.

Applicant however believes that the Examiner likely intended to direct the rejection to claim 57, which does recite a Markush group, and depends from claim 56. Applicant has amended claim 57, as described in the Listing of the Claims, to better define certain preferred embodiments of the invention.

(P) Claims 46 and 48 (Office action, ¶ 53(p))

Applicant has amended claims 46 and 48, as described in the Listing of the Claims, without prejudice or acquiescence to the Examiner's arguments. The above-mentioned amendments to claims 46 and 48 make these rejections moot.

(Q) Claims 19-36, 46, 48-52, 54, 56, and 57 (Office action, ¶ 53(q))

As shown above, applicant has addressed and overcome all of the indefiniteness rejections described in Office action ¶¶ 53(a)-(p) over the pending claims, and in particular over rejected base independent claim 18. Accordingly, applicant respectfully requests that all of the indefiniteness rejections set forth in Office action ¶¶ 53(a)-(q) be withdrawn.

Summary

The applicant respectfully requests reconsideration of the pending claims in view of the amendments and remarks presented herein. The applicants believe that the amendments and remarks presented overcome all of the Examiner's stated arguments and concerns. Should the Examiner have any questions concerning this application, he is invited to contact the undersigned.

Respectfully submitted,

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Clinically Relevant Vaccine-Vaccine Interactions

A Guide for Practitioners

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Contents

Summary

The need for combination vaccines has been recognised for many years. Many children must have 9 or 12 injections in their first year, which places a considerable burden on the child and the health service. Combination vaccines or simultaneously administered vaccines need to generate a protective immune response to all vaccine components that is equivalent to the response when administered separately. This is not always the situation. Many vaccines should not be administered together because of adverse reactions known as vaccine-vaccine interactions, a phenomenon where one vaccine affects another vaccine, thus potentially causing loss of immunogenicity, loss of protective efficacy or induction of adverse reactions. It is important to remember that most vaccine-vaccine interactions are asymptomatic and may only be discovered when the immune status of the vaccine recipient is analysed or when the individual is challenged by the microbe. The interactions may occur because of physical or chemical interactions within the vaccine formulation, interactions between live vaccines or immunological interference. This review summarises known vaccine-vaccine interactions that have been critically analysed and categorised based on their clinical importance.

Children and travellers commonly receive 2 or more vaccines concurrently; indeed, a child may receive up to 6 vaccines simultaneously [diphtheria toxoid, tetanus toxoid and acellular pertussis (DTaP) + *Haemophilus influenzae* type b (Hib) + inactivated poliomyelitis virus (IPV) + hepatitis B (HBV)]. The reasons for combination vaccines are many; one reason is that it decreases the number of injections and visits to the doctor, which results in less discomfort for the child and the parent. Another reason is that it lowers the overall cost of immunisation programmes. However, simultaneous use of vaccines may give rise to adverse reactions called vaccine-vaccine interactions, a phenomenon in which one vaccine may affect the response of another vaccine. Vaccines may also interact with immune globulins and drugs,[1-3] but this paper will solely discuss the present knowledge about vaccine-vaccine interactions.

There is a common misunderstanding among many clinicians that most vaccines may easily be administered together or even mixed together, if possible. Very little attention is paid to vaccine-vaccine interactions, probably because the interactions are usually asymptomatic and may only be discovered if the immune status of the vaccine recipient is analysed. We must distinguish between simultaneous immunisation, when the vaccines are administered separately but simultaneously at different sites, and combined immunisation, when the vaccines are physically combined together in 1 formulation. Good examples of successfully combined vaccines are the 23-valent pneumococcal polysaccharide vaccines, the trivalent poliovirus vaccines and the annual mixture of 3 influenza vaccines (which was first approved in 1945). Combined vaccines may also contain antigens from different pathogens, such as the combined diphtheria, tetanus and pertussis vaccine (DTP), which is the oldest combination vaccine having demonstrated efficacy for over 40 years, and the measles, mumps, and rubella vaccine (MMR). An example of vaccines administered simultaneously, but at different sites, is the combined DTP vaccine and the *Haemophilus influenzae* type b vaccine (Hib).

Throughout history, the various benefits of combined vaccines have been recognised. They are more economical in terms of product cost, healthcare personnel time and simplifying medical record maintenance. For the vaccine recipient it is more convenient, because there are fewer injections and fewer visits to the physician or clinic. The ultimate goal would be the development of a single vaccine that would, with 1 dose, immunise a child for life against all vaccine-preventable diseases.[4] We still have a long way to go to reach that goal. For example, Gambian children must have 9 injections in their first year of life, which places a considerable burden on the health service. With the introduction of the Hib vaccine as a separate injection, it brought the number of injections in the first year up to 12,[5] which is traumatic for the child. These frequent injections are not conducive to compliance. Especially when new vaccines are introduced, it will be desirable to avoid the need for extra visits to the doctor and more injections will mean slower adoption of newly developed and recommended vaccines. At present it may be possible to administer 7 vaccines during 1 clinic visit, with 2 injections (DTP and MMR) and 1 dose of oral poliomyelitis vaccine (OPV).[6]

Although some vaccine-vaccine interactions affect the immune response, the interaction is not associated with any clinical risk for the vaccine recipient. For clinicians and other professionals, it would be an advantage if interactions could be classified based on their clinical importance and frequency. An example of a major and well documented interaction is the concurrent use of OPV and oral RIT 4237 rotavirus vaccine, where the OPV may reduce the seroconversion rate for rotavirus.[7] The time between 2 vaccinations is also an important factor which should not be forgotten, such as the optimum time between administration of 2 interacting vaccines or the time until an interaction may be observed.

Easily accessible information on vaccine-vaccine interactions is extremely important from a public health perspective. It is never the intention to cause 'false security', by administering 2 or

more vaccines simultaneously with the risk that one of the vaccines may be ineffective.

1. Mechanisms of Vaccine-Vaccine Interactions

Combination vaccines or simultaneous administration of vaccines need to generate a protective immune response that is equivalent to their response when administered separately. There are several possible causes for reduced immunogenicity of combination or simultaneously administered vaccines. These include:

- physical or chemical interactions
- interactions between live viruses
- immunological interference.[5]

Physical interactions may affect stability, consistency and immunogenicity. Excipients from 1 vaccine may not prove compatible with those of another vaccine. Vaccines, such as diphtheria toxoid, which are adsorbed to aluminium hydroxide lose their immunogenicity if phosphate is added to the solution because the binding of the antigen to the adjuvant is lost. Figure 1 shows that loading (adsorption) of antigen to aluminium hydroxide is highly critical and overloading may cause poor immune response, which may be one of the possible interactions found when many antigens are mixed together in the same formulation. Similarly, phosphate ions may remove the vaccine from its binding sites, causing loss of immune response. The veterinary vaccine against foot-and-mouth disease loses its immunogenicity if the pH drops below 6.5, and some vaccines contain thiomersal which destroys the potency of inactivated poliovirus vaccine.

Usually, interference between inactivated vaccines is rare, but live vaccines can clearly interfere with each other, especially viral vaccines. When live viral vaccine starts to replicate, it stimulates local interferon production, which may inhibit the replication of another virus. This is the case in the gastrointestinal tract when polio and rotavirus vaccines are administered together orally. Even after the administration of the trivalent oral polio virus vaccine, a competition between virus strains occurs, in which type 2 replicates faster than types 1 and 3.[8] When the MMR vaccine was developed, more immunogenic strains or higher viral doses were required to overcome interference with virus immunogenicity.[9]

Although many live vaccines do interfere, this should not be generalised for all vaccines. It has been shown, for example, that a combined injectable yellow fever and *Salmonella typhi* vaccine is safe and effective.[10] An active enterovirus infection may also interfere with a normal oral vaccination e.g. with OPV.[7] In such situations, revaccination is necessary to confer immunity.[11]

Immunological interactions between different vaccine components are still difficult to understand. There are several theoretical possibilities, involving antigen capture, processing, presentation, or lymphocyte recognition and responses.[8] The increasing use of proteins such as diphtheria and tetanus as carriers for multiple polysaccharide conjugates[12] and cholera toxin B subunit for mucosal vaccination[13] may lead to excessive antitoxin production and epitope suppression of antipolysaccharide responses. Other problems may result from competition for binding sites on an adjuvant molecules, limiting the amount of different antigens in the same formulation. Therefore, new vaccine combinations need to be carefully considered before entering the market.

There are clinical factors that limit the amount and type of combinations available in 1 vaccine formulation. Clinical results have shown that the immunological response to antigens in combination depends on the other antigens present in the vaccine, and it appears that not all vaccines are equivalent.[14] Theoretically, antibody responses to each vaccine may be impaired if 2 or more vaccines are given closely together, possibly through antigenic competition. The mixing of antigens, without consulting the manufacturer, may therefore result in decreased or even eliminated immunogenicity. However, a slight decrease in immunogenicity may be acceptable, as long as the protective efficacy of the vaccine is preserved and the antibody titres correlate with clinical protection.

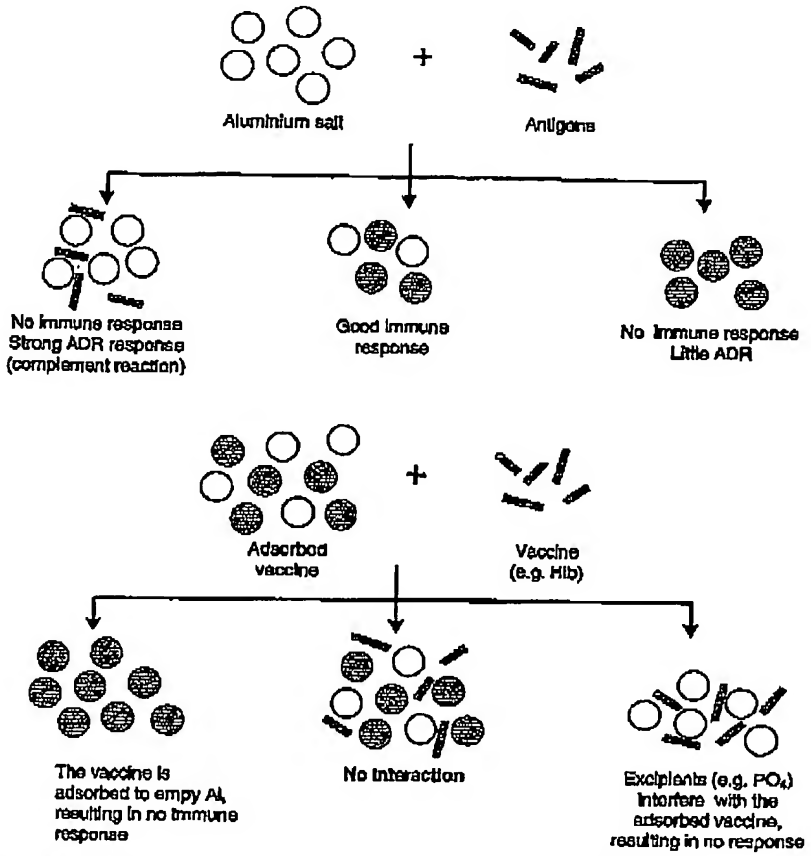

Fig. 1. Loading (adsorption) of antigen to aluminium hydroxide is highly critical for the immune response. Response is dependent on adsorption on the aluminium salt (top), and everything that influences the ratio between loaded and unloaded aluminium salt may affect the immune response, whether it is additional vaccine or foreign materials such as phosphate ions (bottom).

2. Examples of Vaccine-Vaccine Interactions

2.1 Bacille Calmette-Guérin (BCG)

Most vaccine manufacturers who produce bacille Calmette-Guérin (BCG) vaccine recommend that toxoids and killed bacterial vaccines should be administered 7 days before or 10 days after BCG vaccination[2] without adequately justifying their recommendations. However, BCG has been given simultaneously with diphtheria and tetanus toxoids and OPV without any interference,[15] and Labusquiere[16] states that BCG may be administered in association with vaccines for smallpox, yellow fever, measles, smallpox + yellow fever + measles, and tetanus.

2.2 Cholera

2.2.1 Poliovirus

Seroconversion in individuals receiving oral attenuated poliovirus type-1 and also cholera vaccine was significantly lower than in those who received poliovirus vaccine alone. The antibodies to type 2

and 3 poliovirus, however, were not significantly affected by the cholera vaccine.[17]

2.2.2 Yellow Fever

A study by Felsenfeld et al.[18] showed that simultaneous administration of cholera and yellow fever resulted in decreased antibody response to both vaccines. This study was confirmed in 2 Russian studies carried out by Gapochko et al.,[19,20] in which cholera and yellow fever were 2 vaccines among many administered simultaneously. In other studies[21,22] of the effects of simultaneously administered cholera vaccine and yellow fever, the results showed that 30 days post-vaccination the seroconversion to yellow fever started to increase significantly, indicating that simultaneous administration of these vaccines may result in a delayed response.

2.2.3 Other Antigens

The immunogenicity of cholera vaccine may be reduced or lost under the influence of live antigens such as typhus, smallpox and tick-borne encephalitis.[19,20] In contrast, its immunogenicity may be increased if administered concurrently with typhoid vaccine.[19,20]

2.3 Diphtheria-Tetanus-Pertussis

2.3.1 Haemophilus influenzae Type b

Studies of administration of Hib conjugate vaccines simultaneously with DTP have produced controversial results. In most studies, interference has not been seen.[23-27] However, there are several studies in which a depression of both the pertussis and the Hib response was seen.[28,29] In a recent study carried out in Santiago, Chile, 3 groups were given Hib and DTP.[28] The first group received the vaccines mixed together in the same syringe, the second received the two vaccines concurrently but at separate sites, and the last group served as a control group, receiving only DTP. Clear depression was seen in the mixed group for serum anti-Hib and anti-pertussis antibodies. Both of these depressions were statistically significant, but it is not known whether they are of clinical significance or not. Furthermore, the concurrent but separate coadministration also led to a depression of the pertussis response, which came as a surprise to the investigators,[28] especially when pertussis may have a potential adjuvant effect to diphtheria toxoid and tetanus toxoid.[30]

Similar results have been observed in several recent studies using acellular pertussis vaccine, where the problem of interaction may be greater than with whole cell pertussis.[31-35] In a Finnish study by Eskola et al.,[31] the Hib titre was reduced from 3.94 to 0.36 when administered simultaneously with DTaP. However, the pertussis titre was not found to be reduced. When the various acellular pertussis products from different producers are compared, it is surprising to see that no 2 producers use the same dose of each component (table I). This difference may affect the risk of interaction.

Some studies show that the DTP-Hib mixture is able to produce responses to each component that are at least equivalent to, or even higher than, the response to separately administered vaccines from the same lot.[36] These vaccines are normally produced by the same manufacturer and not mixed from 2 separate ampoules.

Table I. Composition (μg/dose) of commercially available acellular pertussis vaccines

Producer	Pertussis toxoid	Filamentous haemagglutinin	Pertactin (OMP)	Agglutinogens
Amvax	40	0	0	0
Biocine	5	2.5	2.5	0
Connaught	5	10	3	5
Pasteur Mérieux	12.5	12.5	0	0
SmithKline Beecham	25	25	8	0
Wyeth-Lederle	3.2	34.4	1.6	0.8

2.3.2 Inactivated Poliomyelitis Virus

In a recent study by Gold et al.,[37] administration of a vaccine containing DTP + Hib + IPV resulted in significantly lower seroconversion against tetanus toxoid relative to a control. In the study by Eskola et al.,[31] IPV was administered simultaneously with DTaP and DTaP-Hib, resulting in a significant and pronounced reduction in the IPV titre for all 3 strains. The clinical relevance of this interaction has not been studied.

2.3.3 Measles

It is unconventional to mix a live virus vaccine with a killed vaccine, but in a study where measles vaccine was mixed with DTP and DTP + IPV vaccine, the measles virus survived the mixing and remained immunogenic for 4 hours, whereafter the immunogenicity declined rapidly.[38] However, the study did not show how this mixing affected other antigens such as diphtheria. A diminished immune response is also seen after concurrent administration, at different sites, of smallpox, yellow fever, measles and DTP vaccine.[39]

2.3.4 Overview

In summary, one may see that when vaccines are physically mixed together, interacting components, such as phosphate ions, may be mixed into the formulation, thus decreasing the immunogenicity of both Hib, pertussis and probably also tetanus and diphtheria. This risk will be eliminated if the same manufacturer produces the final formulation containing these 4 vaccines. Combinations of DTP + Hib with additional components such as IPV, HBV, meningococcal and pneumococcal polysaccharide-protein conjugates are under development.[12]

2.4 Hepatitis B

HBV has been tested in several studies in association with BCG, DTP + OPV, DTP + measles and yellow fever vaccines, in order to ascertain the possibility of including HBV in the child vaccination programme.[40-45] The immunogenicity of each vaccine, injected simultaneously with HBV, was equal to its immunogenicity when injected alone. Recent studies have shown that simultaneous administration of HBV and yellow fever vaccine results in a slightly lower seroconversion rate for yellow fever, but not for hepatitis B.[46] Such an effect was not seen in older studies of simultaneous administration of HBV with BCG and IPV.[42]

2.5 Influenza

2.5.1 Influenza Serotypes

Interactions within influenza serotypes has been seen in 2 studies in which live monovalent and bivalent vaccines (H1N1 and H3N2) were administered to seronegative children.[47,48] The results showed that the frequency of seroconversion was higher when the vaccines were administered individually, rather than simultaneously. However, in a study by Belshe et al.[49] this interference was not observed.

2.5.2 Pneumococcal Vaccine

Influenza has been administered together with pneumococcal vaccine in several studies.[50-53] One of these studies showed that responses to 5 out of 6 pneumococcal types were significantly lower when the vaccines were combined.[53] In most of the studies, however, the efficacy of each vaccine seemed to be unaffected but the adverse reaction rate increased significantly, even though the vaccines were injected into separate sites. In 1 case, small-vessel vasculitis was seen 8 days after immunisation.[54] Since the adverse reactions to the vaccines are usually very mild, it may be concluded that these 2 vaccines may be administered together, but at different sites. Strategies for reducing these adverse reactions and improving the acceptance by older persons (especially high-risk persons) should have priority. They often remain unvaccinated because of the adverse reactions.[55]

2.6 Meningococcal Vaccines

Combining meningococcal groups A and C polysaccharides and attenuated measles into a single vaccine has been studied in children in France. This combination was chosen since a large number of cases caused by these pathogens affected children under 5 years of age. The meningococcal

seroconversion was unaffected, but the immunogenicity of the measles vaccine was significantly depressed.[56]

2.7 Measles

2.7.1 Mumps

In a double-blind controlled study, clinical and serological responses were observed after simultaneous and separate administration of 4 virus vaccines (measles, mumps, poliomyelitis and smallpox).[57] A slight decrease in the seroconversion for mumps was observed, which is in accordance with previously observed data where measles vaccine was found to interfere with the response of live attenuated mumps vaccine.[9] However, the clinical significance of this decrease is small and the simultaneous administration of these vaccines may be regarded safe and effective.

2.7.2 Smallpox

Measles vaccine have been shown to impair the efficacy of smallpox vaccination, although experiments using smallpox, measles and yellow fever vaccine did not show significant results.[34,57-60] It has also been shown that smallpox vaccine can be administered at the same time as a number of other vaccines when injected at different sites.[61] This has been shown when the mixing of smallpox, yellow fever and measles vaccines was conducted before inoculation, showing a diminished immune response to yellow fever when administered to the same site, but satisfactory responses when different sites of inoculation were used.[60]

2.7.3 Yellow Fever

Following the development of live measles vaccines, studies were conducted using a combination of measles and smallpox vaccine and a combined smallpox and yellow fever vaccine. Both combinations were shown to be well tolerated, but mixing of smallpox, yellow fever and measles resulted in diminished immune response to yellow fever.[60]

2.8 Poliomyelitis

2.8.1 Rotavirus

Seroconversion to an experimental oral attenuated rotavirus vaccine (RRV) was found to be reduced from 60 to 10% after simultaneous administration of bivalent OPV.[7] In a study by Migasena et al.,[62] rhesus-human reassortant tetravalent oral rotavirus vaccine was given at the same time as OPV or IPV to Thai infants at 2, 4 and 6 months of age. The results showed that OPV interfered with the response to the first dose of RRV vaccine. After the second and third doses of vaccine, the response rates were not different between the groups. Little or no interference was observed when IPV was used. Similarly, in a study by Ho et al.,[63] a 20% lower level of anti-rotavirus IgA antibodies was seen in infants receiving a single dose of RRV and OPV, compared with those receiving a single dose of RRV alone. In the US, OPV usually contains more virus than is minimally required, which may result in even larger interactions.

2.8.2 BCG

Simultaneous administration of OPV and BCG has been performed without interference, but the manufacturer recommends that vaccinations should occur 3 weeks apart, due to risk of immunological interference,[7,16] without explaining why this concern exists.

2.8.3 IPV-IPV

With respect to the immune response, live virus vaccines clearly interfere with one another, even within the same species of vaccines. When trivalent oral poliovirus is administered, the 3 virus types compete with one another. Antibody development to 1 type occurs after the primary vaccination, but production to all 3 types occurs more frequently after the second dose. Therefore, if the vaccination is to be reliable within the 90 to 100% range, it is important to complete the full 3-dose series of vaccination.[64]

3. Discussion

A summary of vaccine-vaccine interactions, their effects, mechanisms and clinical significance

Table II. Summary of all relevant vaccine-vaccine interactions, including short descriptions of possible clinical effect, which recommendations should be taken, the significance of the interaction (major, moderate or minor) and the quality of documentation, based on literature data

Effector vaccine	Affected vaccine	Effect (mechanism)	Recommendations (managements)	Significance	Documentation
BCG	Diphtheria	Reduced seroconversion	7 days before or 10 days after BCG	Minor	Poor
			Separate doses by 3 weeks		
	Measles	Reduced seroconversion	Separate doses by 3 weeks	Minor	Poor
	OPV	Reduced seroconversion	7 days before or 10 days after BCG	Minor	Poor
	Tetanus	Reduced seroconversion	7 days before or 10 days after BCG	Minor	Poor
	Yellow fever	Reduced seroconversion		Minor	Poor
Cholera	Measles	Antagonistic effects are seen	Separate doses by 3 weeks	Moderate	Poor
		Reduced seroconversion to type 1			
	OPV	Reduced/delayed seroconversion	Separate doses by 1 month	Moderate	Good
	Yellow fever		Separate doses by 3 weeks	Major	Good
DTP	Hib[a]	Reduced seroconversion	Administration at separate sites	Major	Good
	Measles	Loss of immunogenicity	Administration at separate sites	Major	Good
DP + Hib + IPV	Tetanus	Reduced seroconversion	Separate DTP from other vaccines	Minor	Good
DTP + IPV	Measles	Loss of immunogenicity	Administration at separate sites	Major	Good
Hib	Pertussis in DTP	Reduced seroconversion	Administration at separate sites	Moderate	Good
	Tetanus in DTP	Reduced seroconversion	Administration at separate sites	Minor	Poor
Hepatitis B	Yellow fever	Reduced seroconversion	Separate doses by 1 month	Moderate	Fair
Influenzae	Pneumococcal	Increased adverse effects	Administration at separate sites	Minor	Good
Measles	BCG	Reduced seroconversion	Separate doses by 3 weeks	Minor	Poor
	Cholera	Antagonistic adverse effects are seen	Separate doses by 3 weeks	Moderate	Fair
	Meningococcal	Reduced seroconversion of many types	Separate doses by 1 month	Moderate	Good
	Mumps	Reduced seroconversion	Use prepared MMR formulation	Minor	Good
	Smallpox	Reduced seroconversion	Administration at separate sites	Moderate	Fair
	Typhoid	Reduced seroconversion	Separate doses by 3 weeks	Minor	Poor
	Yellow fever	Reduced seroconversion	Separate doses by 1 month	Moderate	Poor
Meningococcal	Measles	Reduced seroconversion	Separate doses by 1 month	Moderate	Good
Mumps	Typhoid	Reduced seroconversion	Separate doses by 3 weeks	Minor	Poor
	Yellow fever	Reduced seroconversion	Separate doses by 1 month	Moderate	Poor
OPV	Rotavirus	Reduced seroconversion	Separate doses by 1 month	Moderate	Good
Pertussis	Hib[a]	Reduced seroconversion	Administration at separate sites	Major	Fair
Smallpox	Cholera	Reduced seroconversion	Separate doses by 3 weeks	Moderate	Poor
	Yellow fever	Reduced seroconversion	Separate doses by 1 month	Moderate	Poor
Tetanus	Hib[a]	Reduced seroconversion	Administration at separate sites	Major	Fair
Typhus	Cholera	Reduced seroconversion	Separate doses by 3 weeks	Moderate	Poor
Tick-borne encephalitis	Cholera	Reduced seroconversion	Separate doses by 3 weeks	Moderate	Poor
Yellow fever	Cholera	Reduced seroconversion	Separate doses by 3 weeks	Major	Good

a When 2 different products are mixed, but not when premixed by a single manufacturer.

Abbreviations: BCG = bacille Calmette-Guérin; DTP = diphtheria toxoid-tetanus toxoid-pertussis; Hib = *Haemophilus influenzae* type b; IPV = inactivated poliomyelitis virus; MMR = measles-mumps-rubella; OPV = oral poliomyelitis vaccine.

is presented in table II. The table separates the affected vaccine from the vaccine responsible for the interaction and describes the possible mechanisms.

While there are many approaches to new vaccine combinations, the focus must remain on administering more effective vaccines more efficiently to the target population. There may be a limit to the number of vaccines that can be physically combined and still be immunologically compatible. Focus should be given to those vaccines having the greatest public health priority.

When the benefits of combined vaccines are evaluated, many questions are raised, such as:

- Do the vaccines given together produce protective effects equivalent to those seen when they are administered separately or at separate times?
- Is there evidence of interference with the immune response?
- Do the products show any interaction, positive or negative, with respect to adverse reactions?[64]

In terms of adverse reactions or safety, there is the opposite concern, i.e. that the sum may be greater than the parts; the combining of vaccines may increase the frequency of existing serious reactions or lead to new reactions.[65] An example of this is the occurrence of local reactions after MMR and DTP and DTP + OPV, separately or simultaneously. The results demonstrated a greater frequency of local reactions after simultaneous administration (23%) than when MMR was given alone (8%).[65] Another issue which seems to be responsible for increased adverse reactions is the fact that more severe injection site reactions have been noted when a vaccine is given to seropositive recipients than to seronegative ones or to those with low seroconversion.[66,67]

New vaccine formulations are increasing and there are numerous studies on different vaccine delivery systems intended for immune augmentation. The same adjuvant may not be suitable for all vaccines. There is some evidence that the pertussis vaccine, along with the aluminium adjuvant, results in an improved response to both diphtheria and tetanus toxoids,[68] although this has not been the case with every combination studied. Formulation of new combination vaccines may, therefore, require adjustment of the adjuvant and/or the antigen concentration, for example when changes are made in the formulation by using acellular pertussis instead of whole cell pertussis.[69]

Many existing vaccine-vaccine interactions are well documented. However, there are several interactions where the manufacturer recommends separation of immunisation although the literature shows little or no interaction. The most controversial interaction is the Hib conjugate vaccines and DTP/DTaP. At present, children in Iceland and Scandinavia receive DTP and Hib vaccines at the same time but in separate doses at different sites. This vaccine will be more acceptable in developing countries if the components are mixed together in the same syringe, reducing cost and minimising the number of injections for each child. However, when acellular pertussis vaccines are marketed in combination with DT, it may be necessary to measure seroconversion in those children who received whole cell pertussis during their primary DTP vaccination. This is because acellular pertussis vaccination used in combination with DT has been shown to give a different level of protection compared with whole cell pertussis vaccination in combination with DT.[70]

In conclusion, new vaccine combinations entering the market as combined vaccines in a single syringe have been tested by the manufacturer for interaction and may therefore be regarded as safe and efficacious. *Ad hoc* mixing of vaccines from different syringes should never be done because it may result in increased adverse reactions and elimination of the immune response to one or more of the vaccine components in the mixture.

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